REMARKS/ARGUMENTS

Reconsideration of this application is requested. Claims 20-29 are in the case.

I THE ANTICIPATION REJECTION

Claims 13, 14 16-23 and 25-28 stand rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Granger, EP 466 650. That rejection is respectfully traversed.

Claims 13-19 have been canceled without prejudice. The anticipation rejection as applied to those claims has accordingly been rendered moot.

The claims in the case are claims 20-29. Claims 20 has been amended to further distinguish over the Granger disclosure. Thus, claim 20 now recites oral administration, and also specifies that the average T_{max} has a coefficient of variation (CV%) lower than 70%.

As now claimed the method is for obtaining an average T_{max} of Diclofenac after 5-30 minutes following administration in a human patient in need of such a treatment, the average T_{max} having a coefficient of variation (CV%) lower than 70%. The method comprises orally administering to the patient a pharmaceutical formulation containing Diclofenac in acid and/or salt form together with an alkali metal bicarbonate selected from the group consisting of sodium bicarbonate, potassium bicarbonate and mixtures thereof and customary excipients and adjuvants, wherein the alkali metal bicarbonate is present in an amount of from 20 to 80 % by weight based on the weight of Diclofenac.

Basis for oral administration appears, for example, at page 3, line 4. Basis for the statement that the average T_{max} has a coefficient of variation (CV%) lower than 70% appears for example at page 2 line 15 where it is stated that, for prior formulations, the coefficient of variation is normally 70-90%, and at page 5 lines 2 and 3 where it is stated

that the coefficient of variation for the present formulations is lower than for the prior formulations on the market. From this, it is believed clear that the CV% of the present formulations is lower than 70%. New claim 29 is based on claim 28 but is dependent on claim 20. No new matter is entered. Entry of the claims presented herewith is respectfully requested.

Referring to Granger, that reference describes various non-steroidal anti-inflammatory agents (NSAIDs) which operate systemically through inhibition of the biosynthesis of prostaglandins, particularly PGE_2. Granger notes that NSAIDs of this type fall into various classes based broadly on structure. Csaky and Barnes describe such NSAIDs as including, amongst others, fenamic acid derivatives, indene derivative, and ibufenac derivatives. At line 10 on page 2, Granger describes the broad classification of fenamic acid derivatives. Granger notes that fenamic acid derivatives are broadly classified as o-anilino derivatives of benzoic, phenylacetic, and nicotinic acids, and are defined by Csaky and Barnes as including flufenemic acid, mefenamic acid, meclofenamic acid, clonixeril, clonixin, flunixin, and diclofenac, as well as pharmaceutically-acceptable salts thereof (page 2, lines 10-12).

At page 2, beginning at line 13, examples of indene derivatives are described, and at page 2, beginning line 19, examples of ibufenac derivatives are described. At page 2, beginning at line 36, Granger refers to the use of a non-toxic prostaglandin-stimulating metal base or basic salt in the manufacture of a medicament in the treatment of inflammation and states, at page 2, line 48, that the metal can be aluminum, magnesium, sodium, potassium, or bismuth. Granger also states that the

metal base or basic salt can be the hydroxide, sulfate, carbonate, bicarbonate, subcarbonate, or trisilicate (page 2, lines 48 and 49).

The list of possible NSAIDs which can be used according to Granger comprises at least 34 different drugs (see page 2, lines 10-22). With regard to the metal, this can be aluminum, magnesium, sodium, potassium, or bismuth, and the metal base or basic salt may be the hydroxide, sulphate, carbonate, bicarbonate, subcarbonate or trisilicate. Aluminum hydroxide is the preferred material, as can be seen from the Abstract and from the working examples. In particular, it is noted that there is no disclosure in the working examples of the use of diclofenac in combination with an alkali metal bicarbonate and, in particular, with sodium and/or potassium bicarbonate.

Granger thus discloses formulations consisting of (1) a NSAID selectable from at least 34 different possibilities, (2) a metal selectable from at least five different possibilities and (3) a base or salt selectable from at least six different possibilities. This computes to over 1,000 different possible combinations of components.

Granger provides no disclosure whatsoever relating to dissolution profiles or hematic levels which can be obtained by administering an oral formulation containing one of the possible disclosed combinations. Granger does not address this issue. Granger, as conceded at page 3 of the action, relates to conferring a cytoprotective effect or reducing gastrointestinal inflammation.

The method as now claimed in this application is not anticipated by Granger. As conceded on page 3 of the outstanding Action, Granger does not disclose T_{max} or C_{max} values. Moreover, as demonstrated by the Declaration evidence presented with the Response dated September 18, 2002 (hereinafter the Reiner declaration), the T_{max} and

C_{max} values are not inherently achieved in view of the Granger disclosure. That Declaration evidence establishes the lack of any inherent disclosure in Granger so far as the presently claimed method is concerned[1]. As demonstrated beginning on page 3 of the Reiner Declaration, Figure 1 depicts the dissolution curves for matrix tablets containing potassium bicarbonate (FII), magnesium carbonate (FIII) and calcium carbonate (FIV), in comparison with control unbuffered matrix tablets FI. The differences in the dissolution properties are striking. The same can be said for the results presented in Figure 2 shown on page 4 of the Reiner Declaration. Figure 2 shows dissolution curves for the matrix tablets containing potassium bicarbonate (FII), magnesium hydroxide (FV) and aluminium hydroxide (FVI), in comparison with the unbuffered matrix tablets (FI). Again, the differences in dissolution profile are striking, further evidencing not only surprising results, but also a lack of predictability and thus lack of inherency with respect to the various possible combinations falling within the range of disclosure. The Reiner declaration thus establishes that while Granger encompasses bicarbonate, there is no recognition that the particular bicarbonate forms employed according to the present invention would give the unexpected results as demonstrated. In addition, in paragraph 7 of the Reiner declaration, it is concluded that formulations according to the present invention provide a more rapid dissolution of diclofenac than the formulations disclosed by Granger and, thus, provide for better pharmacokinetic profiles.

[1] The undersigned has been advised that while the amount of potassium bicarbonate in the tablet of the present invention (FII) falls within the claimed range (20-80wt%), this is not the case for the other tablets (FIII to FVI) although the equivalents of the buffering agent correspond to those of FII.

As yet further evidence that Granger does not disclose (or suggest) the presently claimed invention, attention is directed to the attached executed declaration by Professor Marzo (hereinafter the Marzo declaration). As stated in paragraph 1 of the declaration, Professor is the Head of the Clinical Pharmacology Department at IPAS SA (Institute for Pharmacokinetic and Analytical Studies) and is Lecturer of Pharmacokinetics at the Universities of Milan and Parma. As is clear from Professor Marzo's CV, he is a skilled scientist in this area and is well qualified to make the attached declaration.

Following a brief historical survey of data relating to studies with Diclofenac (paragraphs 5-8 of his declaration), Professor Marzo reverts to more recent data published by Marzo et al. and by Reiner et al. As noted in paragraph 9 of the Marzo declaration, Table 2 attached to the Marzo declaration summarizes the results of trials testing APR formulations in several pilot and comparative bioavailability studies on healthy volunteers against immediate-release reference formulations, already on the market, with particular evidence on time to peak (t_{max}) and related coefficients of variation (CV%). The composition of the tested formulations is reported in Table 3; in particular, the APR formulations used in Trials 1 and 2 correspond to that disclosed in Example 12 of the present application, the APR formulations used in Trial 6 correspond to those disclosed in Example 13 of the present case and the APR formulations used in Trial 3 correspond to those disclosed in Example 14 of the present case. No comparison was carried out against Granger because Granger does not disclose any formulation based on diclofenac.

Professor Marzo notes, in paragraph 10 of his declaration, that Table 1 shows that times to peak obtained with formulations according to the present invention (APR) are shorter than those described with tablets, suspensions, dispersions or solutions by other authors. Table 2 shows that the t_{max} for the APR formulations always occurred within 0.5hr, irrespective of the nature of the salt (potassium or sodium), or the nature of the formulation (solid or solution), whereas the reference formulations always showed t_{max} later than 0.5hr, and for each trial the CV% for the APR formulation was always lower than that for the reference formulation.

Professor Marzo concludes (paragraph 13) that the observed lower inter-subject variability (CV%) associated with the APR formulations results in a better reproducibility of the rate of absorption expressed by t_{max} from one subject to another as compared to the reference formulations (Table 2). The CV% was markedly lower with all APR formulations (between 0% and 60%) than the CV% of the reference formulations, which ranged between 45.2% and 104.7%.

In paragraph 14, it is noted that only in one case the CV% of the APR formulations was higher than 60% - the case of the 50 mg tablet formulation of trial 4 (which exhibited a CV% of 78%). Professor Marzo explains that such a result was due to a problem in the physical characteristics of a batch and it is not representative; the trial was repeated and resulted in a CV% of 60% (trial 8).

In paragraph 15, Professor Marzo discusses Figure 1 (showing frequency of occurring t_{max} with APR's test formulation (Test 2 tablet) and Novapirina (reference)). The highest frequency of t_{max} occurring at 0.33 hr (20 min) was detected in more than 80% of the cases with APR's formulation, and only in 50% of the cases with the

reference formulation. Furthermore, Professor Marzo notes that the t_{max} for the reference formulation occurred up to 2.5 hr, showing high dispersion of the data, while the t_{max} for diclofenac sodium 25 mg tablets by APR occurred not later than 0.5 hr.

In paragraph 18, Professor Marzo confirms that there is no disclosure in the Granger working examples of the use of diclofenac in combination with an alkali metal bicarbonate and, in particular, with sodium and/or potassium bicarbonate. Professor Marzo also states that Granger provides no disclosure relating to dissolution profiles or hematic levels which can be obtained by administering an oral formulation containing one of the possible disclosed combinations, and no disclosure (or suggestion) of improving the absorption of diclofenac with low CV% values.

In light of the above, and in light of the Reiner and Marzo Declaration evidence, it is clear that Granger does not anticipate the presently claimed invention. Withdrawal of the outstanding anticipation rejection is in order, and is respectfully requested.

Allowance of the application is awaited.

Respectfully submitted,

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